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Swiss national prospective surveillance of paediatric *Mycoplasma pneumoniae*-associated encephalitis

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Summary

OBJECTIVE: To assess the presence of *Mycoplasma pneumoniae*-associated encephalitis in children in Switzerland and its likely pathogenesis.

METHODS: *M. pneumoniae*-associated encephalitis cases seen at a single-centre during 2010–2013 were reviewed, and the Swiss Paediatric Surveillance Unit (SPSU) prospectively conducted a nationwide surveillance 2013–2015. Case definition included confirmed, probable and possible cases.

RESULTS: Seven patients (median age 8.7 years, range 4.7–10.1 years) with confirmed or possible *M. pneumoniae*-associated encephalitis were observed. All patients manifested prodromal respiratory symptoms over at least 5 days and five out of the six who had a chest radiograph, showed pulmonary infiltrates. *M. pneumoniae* DNA in cerebrospinal fluid was negative in all patients. Intrathecally synthesised *M. pneumoniae*-specific immunoglobulin (IgM and IgG) were investigated and found positive in one patient (confirmed case). *M. pneumoniae* DNA in respiratory specimens and/or *M. pneumoniae*-specific IgM and IgG in serum were detected in the other six patients (possible cases). One confirmed and two possible cases had neurological sequelae at 4–19 months follow-up.

CONCLUSION: The lack of detectable *M. pneumoniae* DNA in cerebrospinal fluid of our encephalitis patients suggests a likely immune-mediated pathogenesis ignited by a respiratory inflammatory process including pneumonia.

Key words: children; encephalitis; epidemiology; *Mycoplasma pneumoniae*; pneumonia

Introduction

Encephalitis is the most severe extrapulmonary manifestation of *Mycoplasma pneumoniae* infection [1]. Its pathogenesis is not understood [2]. Detecting *M. pneumoniae* in the central nervous system (CNS) may be most straightforward to confirm *M. pneumoniae*-associated encephalitis [3]. However, two large recent national encephalitis studies

were unable to detect *M. pneumoniae* DNA by means of polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) (United Kingdom 2005–2006 [4] and France, 2007 [5]). In contrast, another national encephalitis study reported *M. pneumoniae* as a possible cause, detected either by serology or positive PCR in respiratory specimens, in 6% (96/1570; US, 1998–2005 [6]), compared with two cases confirmed by PCR in CSF (0.1%). Thus, CNS infection or immune-mediated pathology are debated. These divergent pathogenetic hypotheses create uncertainty in diagnostic procedures and lead to differences in case definition criteria [7].

We aimed to assess the presence of paediatric *M. pneumoniae*-associated encephalitis in Switzerland and its likely pathogenesis.

Methods

Study design

Preparatory study

To evaluate whether a nationwide surveillance was worth being conducted we retrospectively reviewed paediatric *M. pneumoniae*-associated encephalitis cases in the frame of a community-acquired pneumonia study at the University Children's Hospital of Zurich [8] between July 1, 2010 and June 30, 2013.

National prospective surveillance study

Between July 1, 2013 and June 30, 2015, the Swiss Paediatric Surveillance Unit (SPSU), a national network of 33 hospitals [9, 10], prospectively collected reports of paediatric *M. pneumoniae*-associated encephalitis. Anonymised demographic, clinical, and microbiological data were sent to the SPSU central, which forwarded the forms to the principal investigator who verified the case definition. An outcome evaluation questionnaire was dispatched to the caring practitioner half a year after case presentation.

***Mycoplasma pneumoniae*-associated encephalitis case definition**

Children ≤ 16 years of age fulfilling (1) the clinical case definition for acute encephalitis (suppl. table S1) [11] and (2) the aetiological case definition for acute encephalitis caused by *M. pneumoniae* [3], i.e., (2a) “confirmed” (detection of *M. pneumoniae* by PCR in CSF or of intrathecal synthesis of specific antibodies), (2b) “probable” (≥ 4 -fold rise in specific serum antibody titre), or (2c) “possible” (detection of *M. pneumoniae* by PCR in respiratory specimens

and/or single raised specific serum antibody titre), were considered cases.

Results

One “confirmed” and three “possible” paediatric *M. pneumoniae*-associated encephalitis cases were observed during the 3-year preparatory study and three “possible” cases during the 2-year national prospective surveillance study (table 1). All patients were male (median age 8.7 years, range 4.7–10.1). Pleocytosis was present in six cases (86%;

Table 1: Characteristics of seven cases with paediatric <i>Mycoplasma pneumoniae</i> -associated encephalitis.												
No.	Inclusion	Age (y), sex	Prodrome (d), symptoms	Chest radiograph	Aetiological case definition for <i>M. pneumoniae</i> -associated encephalitis ¹					Treatment (duration [d])	Outcome (last follow-up [m])	
					CSF		RS	Serum	Case			
					PCR	Antibodies (IgM, IgG)	PCR	Antibodies (IgM, IgG)	definition [3]			
Preparatory study (2010–2013)												
1	12/2010	4.7, M	5 Fever, rhinitis, pharyngitis, conjunctivitis, mucositis, erythema multiforme, cervical adenopathy ²	Infiltrate	–	ND	–	+ ³	Possible	Cefaclorum (3) Aciclovir (3) Ceftriaxone (3) Clarithromycin (7) IVIg (1) Prednisolone (9)	Normal (4)	
2	01/2011	8.3, M	6 Fever, cough, rhinitis	Infiltrate	–	ND	+	+ ³	Possible	Ceftriaxone (3) Doxycycline (7)	Normal (2)	
3	12/2011	10.1, M	5 Fever, cough	ND	–	ND	+	+ ³	Possible	Aciclovir (3) Ceftriaxone (3)	Normal (1)	
4 [18]	11/2012	8.7, M	21 Cough, rhinitis	Infiltrate	–	+ (intrathecal synthesis) ⁴	+	+	Confirmed	Doxycycline (7) IVIg (1) Prednisolone (5)	Mild residual hemiparesis of the upper extremities, incomplete facial palsy (19)	
National prospective surveillance study (2013–2015)												
5	04/2014	9.3, M	15 Fever, cough, rhinitis	Infiltrate	–	ND	+	ND	Possible	Aciclovir (1) Ceftriaxone (1) Ciprofloxacin (1) Vancomycin (1) Moxifloxacin (8)	Optic disc swelling (6)	
6	09/2014	7.8, M	9 Fever, cough	Infiltrate	–	ND	+	ND	Possible	Amoxicillin (3) Clarithromycin (3) Aciclovir (3) Ceftriaxone (3) Ciprofloxacin (14)	Aggressive behavior, headache (4)	
7	05/2015	8.8, M	7 Fever, rhinitis, pharyngitis	–	–	ND	+	+	Possible	Acyclovir (3) Ceftriaxone (1) Methylprednisolone (3) Prednisolone (14)	Normal (hospital discharge)	

CSF = cerebrospinal fluid; Ig = immunoglobulin; IVIg = intravenous immunoglobulin; ND = not done; PCR = polymerase chain reaction; PS = pharyngeal swab; RS = respiratory specimens.

¹ No case met confirmed or probable aetiological case definition for another infectious agent [3]; negative investigations as follows:

Case 1: PCR CSF: Herpes simplex virus 1/2, enteroviruses; PCR PS: Influenza A, respiratory syncytial virus; Serology: Herpes simplex virus 1/2; CSF and blood: conventional bacterial cultures;

Case 2: PCR PS: respiratory viruses (multiplex PCR); PS antigen test: *Streptococcus pneumoniae*; Serology: tick-borne encephalitis; CSF and blood: conventional bacterial cultures; tuberculin skin test;

Case 3: PCR CSF: Herpes simplex virus 1/2, enteroviruses; Serology: tick-borne encephalitis; CSF and blood: conventional bacterial cultures;

Case 4: PCR CSF: Herpes simplex virus 1/2, enteroviruses, Epstein-Barr virus; PCR PS: Influenza A/B; Serology: *Borrelia burgdorferi*; CSF and blood: conventional bacterial cultures;

Case 5–7: no other potential aetiological agents reported, but no further information according to study design.

² Patient 1 developed pericardial effusion during the course of the disease. PCR assays of pericardial fluid and tissue biopsy for *M. pneumoniae* were negative.

³ Persisting elevated IgM and IgG titres over 4 weeks (patient 1), 8 weeks (patient 2), or 6 weeks (patient 3).

⁴ Three-isotype immunoglobulin reaction (IgM, IgG, and IgA).

median cell number 30/ul, range 8–96) and neuroimaging was consistent with encephalitis in five cases (71%; suppl. table S1). Preceding respiratory symptoms were reported in all patients (median duration 7 days, range 5–21 days) and pneumonia was radiologically confirmed in five of six patients (83%). *M. pneumoniae* DNA was detected in the respiratory specimens of six patients, but not in CSF, and *M. pneumoniae*-specific immunoglobulin (IgM and IgG) in serum of all five tested patients and in CSF of one tested patient. Three patients (43%) still had neurological signs and symptoms at 4–19 months follow-up (table 1).

Discussion

Here, we have documented for the first time the presence of paediatric *M. pneumoniae*-associated encephalitis in Switzerland and gathered indications of an immune-mediated process.

Our three *M. pneumoniae*-associated encephalitis cases observed during the 2-year national surveillance represent an estimated yearly incidence of 0.09 cases per 100 000 population ≤ 19 years of age [12], although underreporting is likely. Nevertheless, the figure is comparable to that in Finland, estimated after a national surveillance in 1993–1994 (0.1 cases per 100 000) [13]. The incidence, however, depends on the presence or absence of epidemics. Indeed, we retrospectively identified four patients in a single-centre over a prior 3-year period and three of them coincided with the *M. pneumoniae* epidemic in Europe from 2010–2011 [8, 14].

M. pneumoniae was found as the cause of 9% (84/906; USA, 1998–2006 [15]) and 31% (50/159; Canada, 1994–1998 [16]) of cases of paediatric encephalitis, whereby 2% (1/62) [15] and 12% (6/50) [16] of the cases, respectively, were confirmed by PCR in CSF. The yearly incidence of paediatric encephalitis in developed countries is about 10.5 cases per 100 000 children [13]. Since no data on paediatric encephalitis exist for Switzerland we cannot estimate the relative frequency of our *M. pneumoniae*-associated encephalitis cases.

We found no *M. pneumoniae* DNA in CSF of any patient but it was present in throat specimens of all patients except one, and specific serum antibodies were found in all patients tested. This suggests that their encephalitis was likely immune-mediated following respiratory infection. Indeed, all patients had prodromal respiratory symptoms over at least 5 days. Interestingly, a recent study [17] reported that *M. pneumoniae*-associated encephalitis patients with negative PCR for *M. pneumoniae* in CSF showed radiological signs of pneumonia with infiltrates on chest radiograph more frequently than patients with positive PCR in CSF (77% vs 33%). We found infiltrates on chest radiograph in 83%.

Pleocytosis was present in most of our patients and neuroimaging was compatible with an inflammatory process in 71%. This further underscores the likelihood of an immune-mediated pathogenesis in our *M. pneumoniae*-associated encephalitis cases, which was proven by the detection of an intrathecal antibody synthesis in one investigated patient (patient 4) [18]. Antibodies against *M. pneumoniae* have been shown to cross-react with galactocerebro-

sphingolipid (GalC) [19]. GalC is a major glycolipid antigen in the myelin of both the peripheral and central nervous systems. We previously demonstrated, in this specific case, antibodies against GalC in serum and CSF [20], which suggests that these antibodies are involved in the development of *M. pneumoniae*-associated encephalitis [2]. Intriguingly, one patient showed extensive extrapulmonary multiorgan inflammation with additional involvement of skin and heart (patient 1), which required prolonged anti-inflammatory treatment.

In conclusion, we suspect an immune-mediated process in our observed *M. pneumoniae*-associated encephalitis cases. Pneumonia may be an indicator for the remote inflammatory process. The association of encephalitis with *M. pneumoniae* may be increasingly established by expanding diagnostic procedures through the analysis of intrathecal antibodies.

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Supplementary table

Table S1: Clinical case definitions for seven cases with paediatric <i>Mycoplasma pneumoniae</i> -associated encephalitis.									
No.	Inclusion	Age (y), sex	Major criterion [11]:	Minor criteria (≥3 required) [11]:					
				Fever	New onset of neurological signs and symptoms	Pleocytosis (CSF WBC ≥5/ul)	CSF WBC count (cells/ul)	Abnormality on neuroimaging suggestive of encephalitis	Abnormality on EEG consistent with encephalitis
Preparatory study (2010–2013)									
1	12/2010	4.7, M	Decreased level of consciousness	+	Ataxia	–	3	+ (MRI)	+
2	01/2011	8.3, M	Decreased level of consciousness	+	Ataxia Cerebellar mutism Nuchal rigidity Headache	+	38	–	+
3	12/2011	10.1, M	Decreased level of consciousness	+	Altered verbal communication Incontinence (urine and stool) Nuchal rigidity Headache	+	96	+ (MRI)	+
4 [18]	11/2012	8.7, M	Coma	–	Ataxia Ophthalmoplegia Hemiplegia Nuchal rigidity Headache	+	11	+ (MRI)	+
National prospective surveillance study (2013–2015)									
5	04/2014	9.3, M	Decreased level of consciousness	+	Nuchal rigidity Headache Vomiting	+	8	+ (MRI, CT)	ND
6	09/2014	7.8, M	Decreased level of consciousness Personality change	+	Nuchal rigidity Headache Vomiting	(+)	25 (traumatic)	–	+
7	05/2015	8.8, M	Decreased level of consciousness	+	Ataxia Dysarthria Headache Vomiting	+	35	+ (MRI)	ND

CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; MRI = magnetic resonance imaging; ND = not done; WBC = white blood cell.